

[73] 71. (Amended) A method according to claim 57, wherein the cells are hematopoietic stem cells present in the animal [and are selected from the group of hematopoietic cells found] in at least one of bone marrow, cord blood cells, fetal liver cells and peripheral blood cells.

[74] 72. (Amended) A method according to claim [72] 70, [further comprising; causing the compound to] wherein contacting the stem cells with the hedgehog compound includes [by] administering an effective dose of the compound to the animal by any of oral, intradermal, subcutaneous, transmucosal, intramuscular, or intravenous routes.

[75] 73. (Amended) A method according to claim [57] 80, wherein [the first compound is capable of acting synergistically with] the second compound, [so as to] enhances the stimulation of [at least one of] hematopoiesis of the cells by more than the amount of stimulation of hematopoiesis resulting from administration of an identical amount of the second compound in the absence of the hedgehog compound [, endothelial cell proliferation and endothelial cell differentiation].

REMARKS

Claims 57-73 and 80-92 constitute the pending claims in the present application. Misnumbered claims 67-81 are hereby renumbered as claims 65-79, and accordingly the first new claim added herein is presented as claim 80. Support for the amendment to claim 58 can be found on page 22, lines 14-18, and page 21, lines 26-28. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

With respect to the specification, Applicants have added back the material inserted in the previous response, and have provided an abstract of the invention.

Applicants have amended claims 60 and 61 as suggested by the Examiner to correct the spelling error. Applicants submit that the scope of these claims is not narrowed by this amendment.

Claims 57-81 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

With respect to claim 57, Applicants submit that the term ‘WNT compound’ is not unclear in light of the usage of such terms in the specification. The first three paragraphs on page 5 all refer to the use of a compound which is functionally equivalent to a gene product, and page 10, lines 13-16, repeats this language and specifically points out that WNT is one such gene product. Furthermore, the term ‘hedgehog compounds’ is defined on page 11, and this definition comprises compounds functionally equivalent to hedgehog proteins. Taken together, these statements would indicate to one of ordinary skill in the art that ‘WNT compound’, a term syntactically analogous to ‘hedgehog compound’, refers to WNT gene products and functionally equivalent compounds, as contemplated by the specification on pages 5 and 10. Nevertheless, solely to expedite prosecution of the remaining claims, Applicants have removed this portion of claim 57.

Additionally, Applicants submit that the term ‘second compound comprising a TGF- β compound’ is not unclear for not defining what else the second compound comprises. Applicants submit that ‘comprising’ is used frequently in patent claims to define a portion of a recited element, with the understanding, supported by extensive case law, that the element may include other features. That the other features are not explicitly defined is the normal construction of claims employing the term ‘comprising’. One of skill in the art, in order to understand the metes and bounds of the claims, need only understand that the second compound includes a TGF- β compound, as is clearly recited by the claims. However important it may be to a scientist performing the method to know whether the TGF- β compound is the active ingredient with respect to a particular embodiment, the scope of the claimed subject matter is not rendered unclear by the implicit understanding that the TGF- β compound may be coupled to anything else and yet still fall within the scope of the claim. Because the metes and bounds of this term are clear and definite, even though partially undefined, the claimed subject matter is adequately defined. The Examiner’s attention is directed to MPEP 2173.01, which notes that claim language is definite if it “makes clear the boundaries of the subject matter for which protection is sought”,

and MPEP 2173.04, which states that “[b]readth of a claim is not to be equated with indefiniteness.” Reconsideration and withdrawal of this rejection is respectfully requested.

Applicants have amended line 6 of claim 57 as suggested by the Examiner. Applicants submit that the scope of the claim is not narrowed by this amendment.

Applicants have amended the dependency of claim 61 as suggested by the Examiner to correct this obvious error. Applicants submit that the scope of the claim is not narrowed by this amendment.

Applicants have amended claim 62 to clarify how the added limitations are performed in the context of step (b). Applicants submit that the scope of the claim is not narrowed by this amendment.

Applicants have cancelled claims 76-81 solely to expedite prosecution of the remaining claims, rendering the rejection with respect to these claims moot. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

For the reasons provided above, Applicants submit that the pending claims fully comply with 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 57 and 60-81 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent it is maintained over the remaining claims as amended.

The Office Action cites several cases, such as *Fiers. v. Revel*, *Amgen Inc. v. Chugai*, and *Fiddes v. Baird*, for the proposition that the compounds recited in the claims are not adequately described. These cases, however, are inapposite, because the claims considered in those applications were not method claims, as are the pending claims, but were directed to protein and nucleic acid sequences. “Possession”, as contemplated by the written description requirement, refers not to *physical* possession but to *conceptual* possession. The standard for measuring

sufficiency of the written description, as articulated in *In re Gosteli*, 872 F.2d 1008 (Fed. Cir. 1989), was quoted in *Vas-Cath v. Mahurkar*, already cited by the Examiner:

A fairly uniform standard for determining compliance with the ‘written description’ requirement has been maintained throughout: ‘Although [the applicant] does not have to describe exactly the subject matter claimed, . . . the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.’

While *Amgen v. Chugai* stands for the proposition that a nucleic acid is not conceived until the sequence is known, case law does not support the extension of this holding to method claims such as those presented by Applicants. Applicants are not aware of, nor does the Office Action cite, *any* cases holding that a *method* is not conceived until reduction to practice occurs, as the Office Action asserts.

The Office Action further asserts that “one must still be able to envision the class of compounds based on the written description of the specification.” This statement is not supported by case law, either explicitly, or by any cases of which Applicants are aware. The Office Action does not allege that the limitations and features of the claims are not literally supported by the specification. Methods are not subject to the doctrine of simultaneous conception and reduction to practice that applies when nucleic acids and proteins are claimed as compositions of matter. Instead, methods such as those claimed can be conceived independently and are constructively reduced to practice, at the very least, by the filing of a patent application. Applicants submit that the specification as filed fully supports Applicants’ conception of the subject matter of the pending claims at the time of filing of the present application as required by 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 57 and 60-81 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Office Action first asserts that pending claims are not enabled because “[t]here is no showing . . . in the instant application or prior art” of a WNT compound that is both derived from

extraembryonic tissue and able to stimulate hematopoiesis, endothelial cell proliferation, or differentiation in undifferentiated mesodermal cells. Putting aside the question of whether this statement is accurate, this statement is not apparently relevant to any of the pending claims. Claim 57 encompasses the use of a WNT compound to stimulate cells to undergo at least one of hematopoiesis, endothelial differentiation and endothelial proliferation. This claim is enabled whether or not a WNT compound is or is not derived from extraembryonic tissue. Nevertheless, solely to expedite prosecution of the remaining claims, Applicants have removed this limitation from claim 57. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

With respect to the discussion in the Office Action relating to vasculogenesis, Applicants submit that this portion of the rejection is inapposite to the claims as amended. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

The Office Action also asserts that “[t]here are no examples in the specification or prior art that a *Drosophila* hedgehog polypeptide can activate a vertebrate patched receptor or *vice versa*.” Applicants direct the Examiner’s attention to Exhibit A, Chang et al., *Development* 1994, 120, 3339-3353, which indicates that Hh_g-1, a mouse Sonic hedgehog gene, functions in *Drosophila* in a manner similar to the native *Drosophila* hedgehog protein, as described on pages 3344-3347, despite the fact that these polypeptides are only approximately 46% identical. However, because Applicants are unable to determine the relevance of this argument, or of the argument that “there are no examples of... a hedgehog protein binding to and activating any receptor other than ptc”, clarification is respectfully requested if this rejection is to be maintained.

The Office Action cites *In re Hyatt* and *Ex parte Maizel* for the proposition that claim 57 represents a ‘single means claim’ and is thus subject to an undue breadth rejection, Applicants respectfully point out that the claims at issue in these opinions were composition of matter claims, not method claims, as is the present case. Indeed, 35 U.S.C. § 112, sixth paragraph, which relates generally to means claims, distinguishes between apparatus claims, which employ means, and method claims, which employ steps. Clearly the line of reasoning set forth in the Office Action is inapplicable to a method claim such as those presented herein.

The MPEP provides examples of cases where a disclosure was found not to enable method claims. MPEP 2164.06(b). In one case, *In re Goodman*, 11 F.3d 1046 (Fed. Cir. 1993), the claims were found to lack enablement because the invention would not be operative in all plant cells. In another, *In re Colianni*, 561 F.2d 220 (CCPA 1977), the claims were found to lack enablement because the specification did not teach how to select appropriate parameters to successfully practice the method. The Office Action fails to indicate why one of skill in the art would be unable to practice the claimed method with either a hedgehog polypeptide or any other compound that is functionally equivalent to the hedgehog polypeptide. The Office Action does not assert that any compound that is functionally equivalent to a hedgehog protein would not be operative in the presently claimed method. Nor does the Office Action assert that the specification does not teach what quality is necessary for a hedgehog compound to work in the claimed methods. Accordingly, Applicants submit that the cited cases, and indeed cases actually considering the enablement of method claims, do not support the Examiner's position with respect to enablement of the pending claims.

Applicants have amended claim 73 (formerly claim 75) to point out the effect of administering TGF and a hedgehog compound in combination. Applicants submit that the claim as amended comports with the teachings of the specification.

Applicants have cancelled claims 76-81 solely to expedite prosecution of the remaining claims, rendering the rejection with respect to these claims moot. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

Lastly, Applicants submit herewith as Exhibit B abstracts of two recently published papers which discuss effects of hedgehog compounds on hematopoiesis: Dyer et al., *Development* **2001**, 128, 1717-1730; and Bhardwaj et al., *Nat. Immunol.* **2001**, 2, 172-180. These documents provide further support for Applicants' position that the claimed subject matter was enabled as of the filing of the present application.

Nevertheless, solely to expedite prosecution of the remaining claims, Applicants have amended claim 57 to include the limitation of claim 58, which was not rejected on this basis, thereby rendering this rejection moot. Reconsideration and withdrawal of this rejection is respectfully requested.

For the reasons presented above, Applicants submit that the pending claims are enabled throughout their scope.

Claims 57, 62-64, 69, and 76 are rejected under 35 U.S.C. §102(b) as being anticipated by Zeigler et al. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

A rejection under 35 U.S.C. §102 requires that every element of the rejected claim be met in a disclosure in the prior art. In order to establish a rejection of claim 57 and claims dependent thereon, Zeigler et al. would have to disclose, at the very least, contacting a cell with a hedgehog compound or a WNT compound. The Office Action does not establish a reasonable basis for concluding that TPO falls within the scope of hedgehog compounds as this term is defined in the specification, i.e., that TPO is a functional equivalent of a hedgehog protein. Nevertheless, solely to expedite prosecution of the remaining claims, Applicants have amended claim 57 to include the limitation of claim 58, thereby rendering this rejection moot. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

Applicants have cancelled claims 76-81 solely to expedite prosecution of the remaining claims, rendering the rejection with respect to these claims moot. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

For the reasons provided above, Applicants submit that the pending claims are not anticipated or obvious in light of the prior art. Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this Reply, please charge the fees to our **Deposit Account No. 18-1945**. If a fee is required for an extension of time under

37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

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Customer No: 28120
Docketing Specialist
Ropes & Gray
One International Place
Boston, MA 02110



David P. Halstead, Ph.D.
Reg. No. 44,735